

QUICK SUMMARY

for the **BLOOD PRODUCTS ADVISORY COMMITTEE** **83rd Meeting –July 21, 2005**

The Committee listened to the following briefings and updates. Dr. Jerry Holmberg presented an overview of the May 2005 DHHS Advisory Committee on Blood Safety and Availability. Dr. Ann Gaines, FDA followed with a presentation on disseminated intravascular coagulation associated with acute hemoglobinemia following anti-D IGIV administration for idiopathic thrombocytopenic purpura. Dr. Laurence Landow, updated the Committee on safety of albumin, followed by a presentation on the June 2005 Workshop on Biological Therapeutics for Rare Plasma Protein Disorders by Dr. Mark Weinstein. Dr. Alan Williams presented a summary of the July 2005 Workshop on Leukoreduction and along with Dr. Maria Rios, FDA and Dr. Matthew Kuehnert of CDC presented an update on West Nile Virus.

TOPIC 1

Management of Donors and Units that Test Positive for Hepatitis B Virus (HBV) DNA by Nucleic Acid Tests (NAT)

Dr. Robin Biswas introduced the topic and presented the background for bringing this issue to the Committee. After his presentation, representatives from three manufacturers of HBV NAT assays (Roche Molecular Diagnostics, National Genetics Institute and Gen-Probe) gave presentations on: HBV Seroconversion Panel Results and HBV NAT Positive/Serology Negative Donors; Temporal Association of HBV NAT and HBsAg Reactivity in Prospectively Screened Source Plasma Donations and Retrospectively Screened Seroconversion Panels; and Window Period Detection of HBV with the Procleix Ultrio Assay.

The Committee discussed the loss of suitable blood donors due to false positive tests, and the reasons for these false positive tests, such as contamination. There was discussion of the difference between “permanent deferral,” which is deferral based on a particular FDA testing guidance algorithm that does not permit reentry and “indefinite deferral, also based on that particular guidance algorithm, which is a temporary deferral that does permit reentry. Members also commented on concern of improper release of units, current lock down procedures to prevent such a release, and the required destruction of units that could be useful for research.

During the Open Public Hearing portion of the meeting Dr. Roger Dodd, AABB spoke for the American Association of Blood Banks, America’s Blood Centers and the American Red Cross. While he agreed in general with the proposed algorithm, he

encouraged accurate donor counseling messages, along with re-entry of donors testing falsely positive for HBV DNA and anti-HBc.

The Committee then discussed and voted on the following questions:

1. Based on the scientific data, does the Committee agree with FDA's proposal that

- a) **A donor of Whole Blood and blood components for transfusion who tests HBV NAT positive, anti-HBc non-reactive and HBsAg non-reactive or HBsAg repeatedly reactive/not confirmed by neutralization, may be reentered, if after a minimum period of 6 months a sample from the donor tests negative for HBV DNA by individual donation NAT, non-reactive for anti-HBc and non-reactive for HBsAg, and that**
- b) **A donor of Source Plasma for further manufacture into plasma derivatives who tests HBV NAT positive and HBsAg non-reactive or HBsAg repeatedly reactive/not confirmed by neutralization, may be reentered, if after a minimum period of 6 months a sample from the donor tests negative for HBV DNA by individual donation NAT and non-reactive for HBsAg?**

The Committee voted on question 1a: 14 yes votes, 0 no votes and 0 abstained.

The Committee voted on question 1b: 14 yes votes, 0 no votes and 0 abstained

2. Please discuss any alternative approaches FDA should consider.

Committee members recommended that FDA consider options for test results other than those stated above, such as anticore testing for source plasma donors.

TOPIC II

Scientific Basis for Review of Varicella Zoster Immune Globulin (VZIG)

Dr. Dorothy Scott presented the background for bringing this issue to Committee for discussion. Then Drs. Donna Ambrosino and Catherine Hay, from Massachusetts Biologic Laboratories discussed the manufacture, potency testing and the nation's current supply of VZIG. Dr. Philip La Russa, Columbia University gave a presentation on severe varicella zoster disease, correlates of protection, and post-exposure prophylaxis options. This was followed by a presentation from Dr. Mona Marin, CDC, on the Advisory Committee for Immunization Practices recommendations for post-exposure prophylaxis of severe varicella infections. During Open Public Hearings, Dr. Chris Sinclair, Clinical Research Manager for Cangene Corp. indicated that they had a VZIG product that was approved for use in Canada. Mr. Sinclair stated that Cangene Corp. is evaluating the possibility of supplying the U.S. market.

The Committee was presented with the following questions for discussion:

1. Please discuss what laboratory and clinical data would be sufficient to demonstrate efficacy of a new anti-varicella antibody preparation, for prophylaxis of severe varicella infection. In particular, please comment on

a. Which target population(s) would be most informative to study,

Members discussed that immuno-compromised children may not be a suitable for a clinical study since they may be receiving anti-viral drugs and other blood products which would interfere with the trial analysis. In addition, children on chemotherapy may have been previously vaccinated against varicella, and they may have variable levels of underlying cellular immunity, which could further complicate trial analysis.

b. What surrogate markers would be appropriate for assessment of efficacy,

Members discussed that while antibodies are protective along with a cell related immune response it is difficult to determine the effect of the antibody titer in isolation, on viruses that spread cell to cell. A certain titer of VZIG could be associated with clinical endpoints, but the latter are difficult to collect since varicella complications have become rare, and the underlying population is variable with respect to its underlying immune dysfunction. The Committee agreed that well-understood surrogate markers would be desirable. Some discussants felt that a surrogate marker (antibody level) study in immune competent individuals would be less complicated from the standpoint of underlying level of immune dysfunction, and of obtaining a population for study. Committee members stated that they would be comfortable with an accelerated approval-based licensure approach that included comparative (licensed VZIG vs. new VZIG) PK studies in normal, varicella-naïve people, followed by a phase IV study to confirm safety and efficacy of the product in varicella-exposed susceptible subjects.

c. Other considerations for clinical trials. Members stated that a randomized trial was not likely to be possible, due to the low number and variability in the subject population. It was suggested that a registry of patients could be useful to obtain data that may contribute to the understanding of the efficacy of treatments

2. Please comment whether the available scientific data support the use of IGIV or acyclovir as a substitute for VZIG for prophylaxis of severe VZV infection in any clinical settings.

No, the current scientific data do not support the use of IGIV, however, in the absence of further safety and efficacy studies IGIV could be used as a last resort, if VZIG were not available. The committee noted that IGIV has not been studied systematically as a substitute for VZIG, and current products have lot-to-lot variation in anti-varicella antibody levels. In addition, anti-varicella titers in IGIV

may change over time, due to predominance of vaccinated instead of naturally infected donors to the manufacturing pool. Suggestions were made to consider randomized trials showing IGIV equivalency to VZIG. Acyclovir has its appropriate uses, but it is not a substitute for the immune globulins. FDA should encourage the manufacture of VZIG and regulatory options such as technology transfer should be explored. Increased efforts by FDA, CDC and the Red Book were suggested to encourage alternative source of manufacture. Rather than designing new clinical studies an alternative manufacturer of VZIG should be considered. A suggestion was also made to decrease of label use of VZIG and require documentation of its approved use.

TOPIC III

Summary of Topic III Dextran 1 Pre-treatment for Safe Use of Dextran 40/70

Dr. Larry Landow introduced this topic and stated that pre-treatment of patients with Dextran 1 prior to the administration of Dextran 40 and Dextran 70 results in a 35 fold reduction in the incidence of anaphylactoid reactions and a 90 fold reduction in mortality. On 30 October 1984 Promit (dextran 1) was approved for prophylaxis of DIAR. Currently none of the dextran products mentions use of dextran 1 preinjection in its labeling. In fact, many in the medical community are not aware that a product licensed since 1984 can greatly reduce the incidence of serious DIAR. Dr. Karl-Gösta Ljunström, Associate Professor of Surgery, Karolinska Institute, Stockholm, Sweden, presented his dextran research findings from studies conducted in Scandinavia. The presented data supported the conclusion that pretreatment with dextran 1 can greatly minimize the incidence of severe DIAR.

Two speakers presented during the open public hearing for this topic. Dr. Eileen Bulger, University of Washington and Co-PI of Resuscitation Outcomes Consortium, presented arguments favoring use of Hypertonic Saline Dextran (HSD) without pre-treatment with dextran 1. The consortium is performing a study involving use of HSD in trauma patients. They were placed on clinical hold. They stated that that their study is important and requested that they be allowed to continue with it. COL Holcomb, Trauma Consultant to the US Army Surgeon General stated that the consortium's study is important to the US Army. He also requested consideration be given for the study to continue.

Question to the committee: What revisions to the product labeling for Dextran 40 and Dextran 70 would be most appropriated to address the risk of DIAR and the relevance of pre-treatment with Dextran? In particular comment on whether a class labeling change in warranted and what other forms of risk communication FDA should consider to alert the medical community about the risk of DIAR.

The committee discussed the questions and some members recommended to separate trauma from elective surgery on any label warning. After discussion the committee did not vote, but offered comments that for elective surgery, any treatment with Dextran 40 or Dextran 70 should be accompanied with pretreatment with Dextran 1 and their should

be a warning on the labels of these products. Additionally, the medical and pharmacist communities should be advised of this through communication with their national organizations. Committee members additionally commented that the clinical hold on the trauma should be reconsidered.

This quick summary is provided as an unofficial overview of the committee discussions. Please refer to the meeting transcripts for a detailed account of the meeting.